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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,478	KOSUTIC ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-3 are pending

The terminal disclaimers filed 1/6/10 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Pat. Nos. 7084121 and 6770625 have been reviewed and accepted. The ODP rejections of claims 1-2 over 7084121 and claims 1-3 over 6770625 are thus withdrawn.

The amendment filed 1/6/10 which amends claims 1 and 3 has been entered. Claims 4-13 were cancelled by the amendment filed 12/2/05. Claims 1-3 are under examination.

Priority

Applicant's claim [through amendment (filed 1/6/10) of the specification] for priority that instant application is a continuation-in-part of 10235284 filed 9/5/02 (now US Pat. No. 6770625), and is a continuation application (CON) of 10806523 filed 3/23/04 (now US Pat. No. 7084121) which is a CON of 09873777 filed 6/04/01 (now US Pat. No. 6713452), under 35 U.S.C. 120 is acknowledged.

However, neither 10806523, 09873777 nor 10235284 discloses instant method of treating peripheral pain using a mixture of conjugates comprising the first and second oligomers covalently linked to Lys^{11} and Lys^{18} of salmon calcitonin. Thus, claims 1-3 are not granted priority to 6/04/01 the filing date of 09/342364, nor 3/23/04 the filing of 10806523 nor 9/5/02 the filing date of 10235284. Yet, instant invention is entitled to the filed date 6/24/03 of provisional application 60482130, which has full support for claims 1-3.

The response filed 1/6/10 discusses said "priority" issue (paged 4-9), and submits that, in view of the Office reminds applicants that Paget's disease which is a bone disorder with pain, and in view

of that US 7084121 (10806523) and US 6713452 (09873777) at col. 1 (lines 48-65) and col. 47 (lines12-19) disclose treatment of a bone disorder in a subject by administering the pharmaceutical composition comprising a conjugate having two PEG moieties covalently coupled to the calcitonin wherein the bone disorder is Paget's disease, the co-pending applications 10806523 and 09873777 meet 112/1 requirements (page 7, the response). Thus, the response asserts that all instant claims are entitled to the effective filing date 6/4/10 (page 7, 2nd paragraph).

The response also asserts that the claims are entitled to the filing date 9/5/02 of 10235284 (pages 7-9).

The applicants' arguments are unpersuasive because, as discussed above, none of 10806523, 09873777 nor 10235284 discloses instant method of treating peripheral pain comprising administering to a subject in need thereof a mixture of conjugates (engineered calcitonin) comprising the first and second oligomers covalently linked to Lys^{11} and Lys^{18} of salmon calcitonin.

The discussion of treatment of the bone disorder using said pharmaceutical composition comprising the calcitonin (see above) and discussion of that the bone disorder includes Paget's disease and said disease associated with intense pain appear to implicate relation between treating the bone disorder and treating the claimed "treating peripheral pain" through establishing an inherency thereof. MPEP (7.30.01) states that "*the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention*". Since instant specification neither clearly nor concisely describes that treatment of the peripheral pain uses said "engineered calcitonin", and since the inherency (the relation of treatment of Paget's bone disorder to the treatment of the pain thereof) cannot substitute "full, clear and concise" description of instant invention, the specification of 10806523, 09873777 and 10235284 neither adequately describes nor enable the instant method. Therefore, instant application is only entitled to the filed date 6/24/03 of provisional application 60482130, but not the above-mentioned 6/4/10 and 9/5/02.

Maintained-Objection to specification

The objection set forth in the Office action mailed 3/4/09 is maintained because the response filed 1/6/10 does not address said objection.

New-Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; this is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "treating peripheral pain due to bone disorder", which as amended into claim 3 on 1/6/10, is not supported in the specification as originally filed. Applicant can either cancel the new matter or point out specification support for the phrase in the specification as originally.

Maintained-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1 and 3 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 recite "Lys^{11}" and " Lys^{18}" without reciting the corresponding SEQ ID NO. The claimed "salmon calcitonin" as a calcitonin drug broadly encompasses "calcitonin precursor peptides" and "calcitonin analog" (see page 15, lines 14-18, instant specification) wherein residues 11 and 18 of the salmon calcitonin precursor peptides are not lysine (see NCBI (2009, updated) calcitonin 1 precursor – salmon, www.ncbi.nlm.nih.gov/protein/2144645?ordinalpos=1&itool=EntrezSystem2.PEntrez.Sequence.Sequence_ResultsPanel.Sequence_RVDocSum, pages 1-2). Further, the art (Pham et al. (2004) J. Biol. Chem., 2796720-6729) teaches "$Arg^{11, 18}$ salmon calcitonin" (see abstract). Therefore, setting forth said SEQ ID NO is necessary. In the absence of said SEQ ID NO or indication of the native salmon calcitonin, the lysine residue 11 and 18 cannot be unambiguously determined.

The applicants' response to the 112/2 rejection

At pages 10-11, the response filed 1/6/10 asserts that as the specification [0110] has set forth that "the term "calcitonin" means chicken calcitonin, eel calcitonin, human calcitonin, porcine calcitonin, rat calcitonin or salmon calcitonin provided by natural, synthetic, or genetically engineered sources"; and thus the calcitonin structure is clearly defined. Therefore, the response request withdrawal of rejection.

The applicants' argument is found unpersuasive because instant specification defines that salmon calcitonin as a calcitonin drug encompasses the precursor thereof and the analogue

thereof (see above), and becasue the art shows the salmon calcitonin comprising Arginine 11 and 18 instead of Lysine 11 and 18 (see above). Thus, without citing the sequence identifier thereof or indicating that it is a native salmon calcitonin, the claims are indefinite. Therefore, the 112/2 rejection is proper and maintained.

Maintained-Claim Rejections - 35 USC §102(e)

The text of Title 35, U.S. C 102(e) not included herein can be found in the prior Office action mailed 3/4/09.

Claims 1-3 remain rejected under 35 U.S.C. 102(e) as anticipated by Soltero et al. (US 6770625 B2), wherein the fact of intense pain in bone disorder Paget's disease is evidenced by the Yamamoto et al. (US 5059587) (see col. 1, lines 64-65).

In patent claim 62, Soltero et al. teach a method of treating a bone disorder such as "Paget's disease" (see col. 39, lines 56). The method comprises orally administering to a subject in need a pharmaceutical composition comprising "calcitonin (CT)-drug-oligomer conjugate"; wherein CT is salmon calcitonin and wherein the conjugate is in a mono-dispersed mixture (patent claims 62, 76-79 and 81). Said "oligomer" preferably is "polyethylene glycol" (PEG) (see patent claim 80, and col. 24, lines 27, 35 and 36) linked to Lys^{11} and Lys^{18} residues of calcitonin (patent claim 79). Becasue intense pain is associated with "Paget's disease", treating said disease would necessarily lead to treatment of the pain; as applied to instant method of claim 1.

Soltero et al. teach the structure: "Salmon calcitonin-$[CO\text{-}(CH_2)_7\text{-}(OC_2H_4O)_7CH_3]_2$" (see col. 31, lines 3-8) wherein "-$(OC_2H_4O)_7$" is PEG moiety subunits (see col. 25, lines 7-16, this

meets the limitation 7 polyethylene glycol subunits), wherein the portion "CO-$(CH_2)_7$-" is a lipophilic moiety that preferably is a fatty acid moiety (see col. 25, lines 37-40), and wherein "**2**" in outside parentheses "[ ]" indicates that two residues of CT peptide, i.e., Lys^{11} and Lys^{18}, are conjugated to the PEG moieties. This teaches the structural limitation of the "conjugate" of claim 3.

Soltero et al. teach that **a** (one) hydrolyzable bond between drug peptide and the "oligomer" (see col. 33, lines 47-50). In accordance with the claim 38 disclosure that PEG is coupled to the "oligomer" (i.e., calcitonin) via Lys^{11} and Lys^{18} residues of calcitonin, thus, one of these two ε-lysine amino groups is conjugated to the PEG through said "hydrolyzable bond" while the other remains non-hydrolysable. This meets the structure of claim 2 "conjugate". Therefore, Soltero et al. inherently teach instant method of claim 2.

The applicants' response to the 102(e) rejection

At page 11, 3rd paragraph, the response filed 1/6/10 submits that Soltero has 102(e) date back to 9/25/02 whereas instant application has priority 9/5/02 (filed date of 10235284 (see above) according to the petition set forth in "Appendix A" filed 1/6/10. Thus, response infers that Solder's patent is not the anticipatory art, and therefore, requests withdrawal of the 102 rejection above.

The applicants' arguments are found unpersuasive because the instant application is only entitled to the filed date 6/24/03 of provisional application 60482130 (see above section "Priority"). Thus, the Soltero et al. patent is qualified to be the anticipatory prior art against instant claims 1-3. Therefore, the above 102(e) rejection is proper and maintained.

Claim Rejections - 35 USC §103(a)

The text of Title 35, U.S. C 103(a) not included herein can be found in the prior Office action mailed 3/4/09.

[1] Claim 1 remains rejected under 35 U.S.C. 35 U.S.C. 103(a) as unpatentable over as obvious over Lee et al. (US 6506730 B1).

In patent claims 1 and 2, Lee et al. teach a method of treatment a disease comprising administering to mammal in need a pharmaceutical composition comprising polyethylene glycol (PEG) conjugated (PEGylated) calcitonin peptide wherein said calcitonin is obtained from Salmon, and wherein the treatment refers to curing Paget's disease which symptom shows pain (considering a peripheral pain) from the bone absorption (see col. 6, line 24-28). The PEGylation occurs at Lys^{11} and Lys^{18} of calcitonin (see col.5, line 54 and also Example 4 "di-PEG-sCT"), i.e., di-PEG calcitonin. Lee at al. teach a uniformed PEG-peptide conjugate wherein "uniformed" conjugate is equivalent to instant "mono-dispersed mixture conjugate". These are applied to instant claim 1.

Lee et al. do not expressly teach use oral administering rote.

It would have been obvious to one skilled in the art at the time the invention was made to determine the administration route, and/or parameters for suitable/optimal administration. Injection administration gives patients pain and has accompanying dangers; and thus, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.).

Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

The applicants' response to the above 103 rejection

At pages 11-14, the response filed 1/6/10 submits that Lee's Example 4 teaching nothing about PEG conjugated at both lysine residues 11 and 18, and that Lee et al. teach away from instant method using oral administration route (see last paragraph at p.12 to first paragraph at p.14) by discussion of that the nasal transmucosal delivery is significantly improved in absorption efficiency compared with the oral administration and discussion of disadvantage of oral administration as to liver metabolism, i.e., biological instability of the PEGylated calcitonin (p.13, paragraphs 3-5, the response).

The applicants' arguments are unpersuasive because Lee et al. have taught that PEGylation occurs at Lys^{11} and Lys^{18} of calcitonin, i.e., di-PEGylated calcitonin polypeptide (see col.5, lines 53-55 and Example 4), and because the Lee et al, have also taught that the nasal transmucosal delivery needs to be improved, since the absorption efficiency of said delivery is lower that intravenous injection (col. 2, lines 1-6) wherein said delivery requires help of absorption promoters such as surfactant which are difficult to apply in practice and even cause to irritate nasal mucosae (col.2, lines 12-15). These suggest the drawbacks of the nasal transmucosal delivery. Thus, the response addressed "significantly improved in absorption efficiency compared with the oral administration" does not necessarily mean that the nasal

transmucosal delivery is better than oral administration in every aspects. Therefore, the skilled artisan would have tried several administration routes for the treatment including the oral administration discussed above.

In addition, the PEGylated calcitonin like other PEGylated protein/peptide has increased in vivo half-life, i.e., enhanced biologically stability (see col.2, lines 64-67, col.3, lines 12-20). Thus, the liver metabolism (or protein degradation) may not be at issue herein. One of or route or the nasal transmucosal delivery route with successful expectation in order to avoid (i) using absorption promoter (required for said delivery) which has side effect, i.e., causing nasal mucosae irritation and are difficult to apply in practice (see col. 2, lines 12-15, Lee et al.) and (ii) low absorption efficiency thereof (col.2, lines 1-2, Lee et al.). Therefore, the 103 rejection is proper and maintained.

[2] Claim 1 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that calcitonin (CT) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21).

Yet, Russo does not expressly teach use PEGylated CT for treating pain, wherein PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT (claim1), nor expressly teach oral administering route.

Komarova et al. teach PEGylation of CT at Lys^{11} and Lys^{18} residues and teach advantages of the PEGylation of enhance stability, increases half-life and decrease immunogenicity of said CT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), as applicable to claim 1.

Lee et al. teach that injection administration gives patients pain and has accompanying dangers; and thus, there is a need to develop other routes for peptide administration (col. 1, lines 43-48).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PEGylated CT for treating the pain condition, wherein the PEG moiety is conjugated to the CT peptide directly through amino acids Lys^{11} and Lys^{18}. This is because Russo has taught usefulness of CT peptide for treating pain, and becasue Komarova et al. have taught that the CT peptide is PEGylated at of Lys^{11} and Lys^{18} side chains. This Pegylation has advantage over the unpegylated peptide thereof in enhanced stability, increases half-life and decreased immunogenicity (see above). Thus, it would have been obvious for one of ordinary skill in the art to substitute the PEGylated CT for the non-PEGylated thereof with reasonable expectation of success.

In addition, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of

ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

Therefore, the combination of references' teachings renders the claims obvious.

The applicants' response to the above 103 rejection

At page 14, the response filed 1/6/10 submits that the primary reference Komarova et al. do not antedate instant priority date 6/6/03, and asserts that the combined references do not render the claim unpatentable; and thus, requests withdrawal of the rejection.

The applicants' arguments are unpersuasive because the instant application is only entitled to the filed date 6/24/03 of provisional application 60482130 (see above section "Priority"), and becasue Komarova et al. and Lee et al. provide motivations for using the (Lys^{11} and Lys^{18}) PEGylated CT peptide for treating the pain and using oral administration for the treatment, respectively (see above). Therefore, the above 103(a) rejection is proper and maintained.

[3] Claim 2 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273), Katre at al. (US Pat. No. 4917888) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that calcitonin (**CT**) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21).

Komarova et al. teach PEGylation of CT peptide and the advantages of the PEGylation: enhance stability, increases half-life and decrease immunogenicity of said CT peptide, wherein PEGylation occurs at Lys^{11} and Lys^{18} side chains of the CT peptide (see p.265, right col., 2nd paragraph, and Fig. 1). The Russo and Komarova teachings are applied to claim 2.

Yet, Russo and Komarova et al. do not expressly teach attachment of a non-hydrolysable linker between the peptide PEGylated and polyethylene glycol (PEG) nor expressly teach oral administration.

Katre et al. teach the hydrolysable bond between amine group of lysine and PEG moiety in the PEGylated peptide IL-2 (see col. 14, lines 28-36) wherein the amine group is lysine side chain (col. 8, lines 41-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a hydrolysable linker or bond between the peptide and PEG moiety. This is because Russo has taught usefulness of CT peptide for treating pain, and Komarova et al. have taught that the PEGylated CT peptide is advantageous over the unpegylated peptide at least in three aspects: enhanced stability, increases half-life and, and decreased immunogenicity.

The hydrolysable bond between the PEG moiety and lysine amino side chain offers an advantage, i.e., it is particularly useful for recovering the peptide from the chromatographic column wherein the pH value of said column is close each other to that render the bond susceptible to hydrolysis as taught by Katre et al. (see col. 14, lines 28-36). Thus, one of ordinary skill in the art would have extended the Katre's results into production of the PEGylated CT peptides. The produced PEG-CT conjugates would expect to have benefit that the PEG polymer

cane be removed under alkaline condition and thus the CT peptide can be recovered from the hydrolysis.

In addition, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

Therefore, the combination of references' teachings renders claim 2 obvious.

The applicants' response to the above 103 rejection

At pages 14-15, the response filed 1/6/10 argues against the rejection with reasons similar to 103(a) rejection [2] above, and further asserts that Katre et al. do not overcome the shortcoming of other 103 references, i.e., use of the (Lys^{11} and Lys^{18}) PEGylated CT for treating pain by oral administration.

This is found unpersuasive becasue of the similar reasons set forth above for the 103(a) rejection [2], and because, as discussed above, the (Lys^{11} and Lys^{18}) PEGylated CT has been taught by the combined reference Komarova et al., use of the said PEGylated CT for treating the

pain has been taught by the primary reference Russo, and motivation of using oral administration route has been suggested by Lee at el. Here, Katre et al. provide the teaching as to the advantage or usefulness of incorporating the hydrolysable bond between the PEG moiety and conjugated protein (see above). Thus, the combination of the references' teachings renders claim 2 prima facie obvious. Therefore, the 103(a) rejection is proper and maintained.

[4] Claim 3 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73,265-273), Katre et al. (US Pat. No. 491788), Crotts et al. (US 2003/0017203 A1), Ekwuribe N. (US Pat. No. 6638906 B1 cited in the Office action mailed 3/4/09) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that CT therapeutic use in relieving pain, e.g., "hypercalcemia pain" and treating Paget's disease (col. 9, lines 17-21).

Komarova et al. teach PEGylation of CT at Lys^{11} and Lys^{18} residues and teach advantages of the PEGylation of enhance stability, increases half-life and decrease immunogenicity of said CT peptide (see p.265, right col., 2nd paragraph, and Fig. 1). Komarova et al. teach PEGylation of CT peptide and the advantages of the PEGylation: enhance stability, increase half-life and decrease immunogenicity of said CT peptide (p.265, right col., 2nd paragraph) wherein the conjugated PEG polymer has 7 PEG subunits (see Fig.1).

The Russo and Komarova et al. teachings are applied to claim 3.

Yet, Russo and Komarova et al. do not expressly teach attachment of a carboxylic acid as a linker between the peptide and PEG, nor expressly teach oral administration.

Ekwuribe teaches incorporation of a carboxylic acid such as fatty acid (see col. 11, lines 7-8) into between PEG moiety and the PEGylated peptide in order to enable better penetration of the PEGylated peptide through the cell membrane, which is mimic penetration enhancer (see Example section at col. 11, lines 28-32, and lines 37-40 and col. 6, lines 60-67). Ekwuribe further teaches that lipophilic (hydrophobic) portion of fatty acid is distal to the point of attachment to the LCRE peptide (col. 11, lines 7-8); this is an obvious structural variation of the claim 3 limitation as to carboxylic acid is coupled at the end distal to the carboxylic acid moiety to PEG moiety.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a fatty acid (a type of "carboxylic acid) into PEG conjugated the CT peptide between the conjugation sites: Lys^{11} or Lys^{18} of said peptide and the PEG moieties. This is because Russo has taught usefulness of CT peptide for treating pain, and Komarova et al. have taught that the PEGylated CT peptide is advantageous over the unpegylated peptide in at least three aspects: enhanced stability, increases half-life and, and decreased immunogenicity.

It has been known that a biological difficulty for salmon CT to penetrate the mucus membranes which limits bioavailability of the calcitonin (see [0004], lines 11-15, Crotts et al.). Upon reading the Cortts and Ekwuribe reference, one skilled in the art would have realized the problem of bioavailability of the calcitonin peptide caused by the membrane penetration, and realized that bioavailability of the calcitonin peptide caused by the membrane penetration of said peptide, and realized that the incorporated fatty acid in the PEGylated peptide wherein the fatty

acid acts as membrane penetration enhancer is beneficial for the PEGylated CT peptide; and would have known that the incorporation of fatty acid which is known membrane anchor molecule. Ekwuribe has addressed that their inventions is not limited to the "LCRF" peptide but applicable for other therapeutic peptides (see col. 8, lines 30-37), e.g., the CT peptide herein. Thus, one of ordinary skill in the art would have modified the PEGylated CT peptide further to incorporate fatty acid (a carboxylic acid) into said peptide in order to improve the membrane penetration ability of the PEGylated CT.

Additionally, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

Therefore, the combination of references' teachings renders claim 3 obvious.

* *Examiner remark*: the inherent property of the "mono-dispersed" of the PEGylated CT conjugate has been discussed above, which is applied to the above 103(a) rejections [2] and [3].

The applicants' response to the 103 rejections

At page 15, the response filed 1/6/10 argues against the above 103 rejection similar to the 103 rejections [2] and [3] above, and requests withdrawal of the rejection.

The reasons of unpersuasiveness of the applicants' argument have been set forth accordingly under Examiner responses to the 103 rejections [2] and [3] above, since the applicants' argument here is similar to the arguments as to the rejection [2] and [3] thereof. Thus, the above 103 rejection is maintained.

New-Claim Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 11 and 12 of US Pat. No. 6713452 (**'452**).

Although the conflicting claims are not identical, they are not patentable distinct from each other because of the following reasons.

Claims 70, 72, 1 and 15 of '452 disclose a method of treating a bone disorder in a subject wherein the bone disorder is Paget's disease (patent claim 72) which is associated with intense pain in some stage (see col. 1, lines 39-51, '452 specification) comprising oral (see Example 52) administering PEGylated salmon calcitonin wherein the calcitonin peptide is PEGylated at lysine residues 11 and 18 (patent claim 1) wherein PEG moieties have 7 PEG subunit (claim 15), which disclose common subject matter of instant claims 1 and 3.

Claim 8 of '452 disclose further discloses that in the PEGylated calcitonin, the calcitonin polypeptide is linked to the PEG polymer by a hydrolyzable bond. Claims 1, 15, 70 and 72 , together with claim 8 thus are obvious variation of instant claim 2.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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